

**DYSCHROMATOSIS UNIVERSALIS HEREDITARIA A CLINICO-EPIDEMIOLOGICAL
STUDY FOR TWELVE CASES IN AL-RAMADI CITY*****Abdullah Mancy [FICMS (D&V)] and Khalid Mohammad Awad [FICMS (D&V)]**

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ABSTRACT

Background: Dyschromatosis universalis hereditaria is uncommon hereditary disease usually has autosomal dominant inheritance, its pathogenesis is unknown, characterized by generalized asymptomatic hyperpigmented and hypopigmented macules on the trunk and extremities in a mottled appearance. **Objective:** To shed light on the prevalence and clinical presentation of dyschromatosis universalis hereditaria in Iraqi patients. **Patients and Methods:** Patients presenting with features of dyschromatosis universalis hereditaria were studied with their families within period from 2008-2012 in dermatology department in AL-Ramadi Teaching Hospital which serving a population around 0.8 million. In all patients a detailed history was taken and careful physical examination of all patients, regarding skin and other systems were carried out. **Results:** Twelve patients with dyschromatosis universalis hereditaria, six females and six males were studied, their ages ranged from 10 years -54 years old with a mean age 30 years, their age of onset ranged from birth - 15 years with a mean age of onset was 6.25 years. The prevalence was 15/10⁶, the inheritance was autosomal recessive in 83.3%, Consanguinity of patient's parents was present in 91.7%, the cutaneous manifestations were the main complaint which affects the sun protected areas mainly, histopathological examination revealed focal increased melanin deposition within the keratinocytes of the basal cell layer. **Conclusion:** This study had confirmed that dyschromatosis universalis hereditaria is common disease and to remind clinicians about diagnosis of the disease should be kept in mind for patients presenting with generalized mottled dyspigmentation.

KEYWORDS: Mottled pigmentation, autosomal recessive, consanguinity.**INTRODUCTION**

The dyschromatoses are a group of uncommon disorders characterized by the presence of asymptomatic hyperpigmented and hypopigmented macules forming a reticulate or mottled pattern.^[1,2]

The classification of hereditary dyschromatoses depends on the distribution and extent of skin lesions and includes:^[1,3]

- 1- Generalized forms: Dyschromatosis Universalis Hereditaria (DUH) which has been subtyped into DUH 1 (OMIM 127500), an autosomal dominant form, and DUH 2 (OMIM 612715), an autosomal recessive form.^[1,4]
- 2- Localized form: Dyschromatosis Symmetrica Hereditaria (DSH) (OMIM 127400) also called Acropigmentation of Dohi.^[1,5]
- 3- Segmental form, Unilateral Dermatome Pigmentary Dermatitis (UDP).^[4,6]

Dyschromatosis universalis hereditaria is uncommon hereditary disease, usually has autosomal dominant

inheritance which was reported in the majority of cases, although autosomal recessive inheritance and a few sporadic cases have been described.^[1,5]

The pathogenesis of DUH is still not known, the differences in the frequency of this disorder between East Asia and other regions may be due to genetic heterogeneity.^[7,8,9,10] Two loci responsible for DUH have been identified; one on chromosome 6q24.2-6q25.2 in two Chinese families and one on chromosome 12q21-q23 in an Arab population.^[2,7,9]

The histopathological examination typically shows a focal increase or decrease in melanin content of the basal layer (depending on the type of the lesion biopsied) and occasionally pigmentary incontinence with some melanophages and lymphocytes in the upper dermis.^[4,7] The number of melanocytes was normal, there was no abnormality of collagen and no alterations in the reticular dermis.^[2,6,7]

Fontana- Masson stained sections show either heavily-stained melanin pigments in the basal layer of the epidermis with melanophages in the upper dermis or show no melanin pigments and clear basal cells which appear inactive melanocytes, depending on the lesion biopsied whether hyperpigmented or hypopigmented lesion.^[1]

In an ultra-structural study of skin from patients with DUH, showed normal numbers of melanocytes but the amounts of fully melanized melanosomes differed between hyperpigmented and hypopigmented macules.^[6,9,11,12]

Dyschromatosis universalis hereditaria characterized by generalized asymptomatic hyperpigmented and hypopigmented macules of various sizes and shapes seen on the trunk and extremities, including the dorsa of the hands and feet in a mottled appearance,^[2,4] the dyschromia usually present in the first years of life, although in few patients, the onset of the disease was a little later, in about 80% of reported cases, lesions appear before the age of 6 years and approximately in 20% of cases present at birth.^[4,6]

The trunk and the extremities are the dominant sites affected,^[2,4] facial lesions are seen in 50% of affected individuals, and involvement of the palms and soles are unusual, but they can be affected with a diffuse hyperpigmentation interspersed with spotty hypopigmented macules and dystrophic nail changes with pterygium formation were reported.^[1] DUH may have a systemic association and abnormalities of the nails, hair and teeth.^[1,6]

The oral mucosa and tongue are usually spared, but isolated reports have illustrated mucous membrane involvement including the tongue with mottled pigmentation.^[1]

Many associated conditions with DUH have been reported such as high-tone deafness, ocular abnormalities, neurosensory hearing defects, learning difficulties, mental retardation, epilepsy, insulin-dependent diabetes mellitus, erythrocyte, platelet and tryptophan metabolism abnormalities, small stature, tuberous sclerosis and x-linked ocular albinism.^[3,10,13]

PATIENTS AND METHODS

After obtaining a clearance for the study from the institutional ethics committee and an informed consent was taken from all Patients included in the study and Al-Anbar Health Department ethical committee approved obtained, those presenting with clinical manifestations of DUH were evaluated with their families within four years duration from 2008-2012 in dermatology department in AL-Ramadi Teaching Hospital and this hospital serving a population about 0.8 million.

In all patients a detailed history was taken regarding age of the patients, age at onset, residence, clinical features, family history including: number of family members, number of affected, consanguinity of parents, analysis of family pedigree, history of other congenital diseases, medical and drug history.

A careful physical examination of all patients carried out, regarding skin and other systems.

Routine laboratory investigations include blood count, liver function test, renal function test and electrolytes were done.

A skin biopsy was taken from hypopigmented and hyperpigmented lesions of some patients and sent for histopathological examination.

RESULTS

Twelve patients with DUH, six females and six males were studied, their ages ranged from 10 years -54 years old with a mean age 30 years, their age of onset ranged from birth - 15 years with a mean age of onset was 6.25 years. The prevalence was 15/10⁶, from analysis of family pedigrees, the inheritance was autosomal recessive in 83.3%, while sporadic cases without family history was 16.7 % with no autosomal dominant was reported in cases studied and no sex difference. Family history was present in 83.3% of patients studied. Consanguinity of patients parents was present in 91.7%.

Regarding the cutaneous manifestations which consist of asymptomatic hyperpigmented macules of various size admixed with variously-sized hypopigmented macules forming a mottled pattern represent the main complaint in all patients studied, the main site affected was the sun protected areas which include neck, anterior and posterior trunk, proximal upper and lower extremities which affected in all patients while the sun exposed areas such as the face, hands, forearms, feet and legs are spared. "Fig.1" and "Fig. 2".

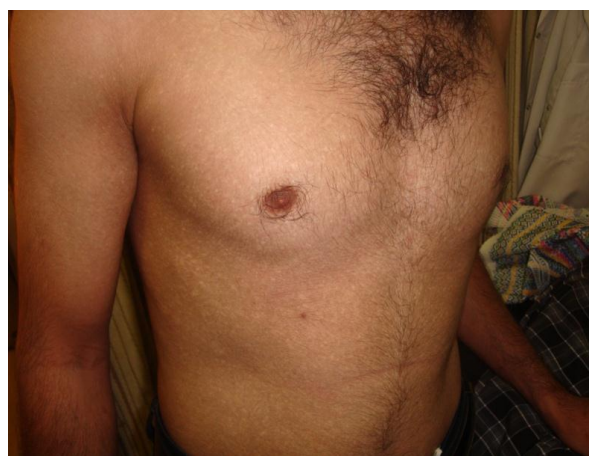


Figure 1: DUH in thirty years old male showing generalized hyperpigmented and hypopigmented macules forming mottled pattern of the anterior trunk.



Figure 2: DUH in twenty years old female patient showing generalized hyperpigmented and hypopigmented macules forming mottled pattern of the posterior trunk.

There was no history of pruritus, photosensitivity or photophobia and no one of the patients studied develop erythema, telangiectasia or atrophy. Nail, hair, teeth and mucous membrane were normal and not affected by the disease, no systemic involvement found and in all patients studied, no history of handling any chemicals or significant drug exposure. All patients had normal mental and developmental milestones. Histopathological examination of the hyperpigmented lesions reveal increased melanin deposition within the keratinocytes of the basal cell layer with pigmentary incontinence and melanophages in the papillary dermis highlighted by Hematoxylin and Eosin [H&E] and Fontana-Masson stain, in contrast, the hypopigmented lesions showed reduced melanin deposition within keratinocytes. "Fig.3" and "Fig.4".

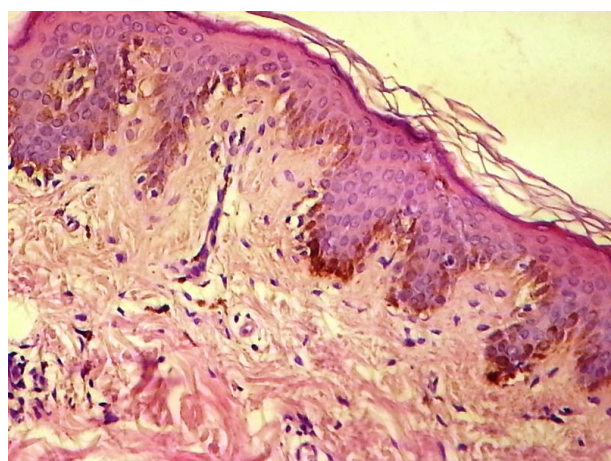


Figure 3: Histological examination of a skin of patient with DUH, with Hematoxylin and Eosin stain, X20, showing focal increase of melanin pigment in the basal keratinocytes.

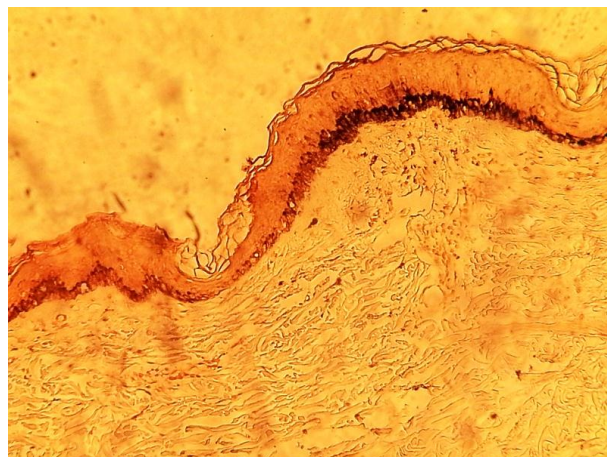


Figure 4: Histological examination of skin of patient with DUH, with Fontana-Masson stain, X10, showing focal increase of melanin pigment in the basal keratinocytes.

DISCUSSION

Dyschromatosis universalis hereditaria seem to be common disease in Iraqi population as was reported in other countries, as the prevalence of the disease in this locality was 15/10⁶ compared to its rarity in other countries,^[1] this may be related to the marriage between close relatives which constitute about 91.7%, and the family size which comprise numerous members of the family.

The dyschromia usually present in the first years of life and in about 80% of reported cases, lesions appear before the age of 6 years,^[4,6] but in the present study there was a later age involvement, mean age 30 years and mean age of onset 6.25 years, this may be related to the fact that DUH is asymptomatic disease and it affects the covered parts of the body which may lead to delayed medical advice by parents.

It has been reported that there is a slight female preponderance,^[1,6] but in patients studied, there was equal sex affection and this may be related to the small number of the patients and in 83.3% was autosomal recessive in which male and female are equally affected.

The reported inheritance pattern of DUH is variable with autosomal dominant mode described in the majority of cases, in addition to sporadic and autosomal recessive mode^[1,6] while in cases studied, after analysis of family pedigrees, the majority was autosomal recessive mode of inheritance which forms about 83.3% and sporadic in about 16.7 %, this may be related to high rate of consanguinity in marriage between families which form 91.7 %. In the present study, the main affected sites were sun protected areas which is neck, trunk and proximal extremities while sun exposed areas like face, hands and feet were not affected, this may be due to genetic heterogeneity of the disease and may indicate the protective effect of sunlight which may has a role in the treatment.

There is report indicate involvement of mucous membrane, tongue, palm and sole,^[1] but no such association has been found in our cases and there was no abnormalities of nail, hair and teeth or systemic associations. Also there was no complain of pruritus, photosensitivity or photophobia and the main complain of patients studied was cosmetic appearance of the

disease. The diagnosis of DUH rely mainly on external phenotype because the Gene candidate for chromosome 6 or 12 (which contain the Gene loci responsible for DUH) have not been definitively identified.^[6] There are many dermatoses in which the dyschromia is a major complaint, the most important described in the table [1].

Table 1: Differential diagnosis of dyschromatoses.

Disease	Clinical features	Associations
Dyschromatosis universalis hereditaria ^[1,2,4,5,7]	<ul style="list-style-type: none"> • AD mainly, AR occasionally. • Early childhood. • Mottled hyperpigmented and hypopigmented macules on the trunk, limbs, face, over almost all the body. • Pigmentary incontinence with increase or decrease in melanin contents of the keratinocyte of the basal layer, normal melanocytes number. 	Hair, nail and mucous membrane abnormalities and systemic association may be present.
Dyschromatosis Symmetrica Hereditaria ^[2,5,6,14,15,16]	<ul style="list-style-type: none"> • AD • Infancy and Occasionally childhood. • Mottled hyperpigmented and hypopigmented macules on. • On dorsum of hands, feet and face. • Pigmentary incontinence with increase or decrease in melanin content of the keratinocyte of the basal layer, normal melanocyte number . 	None
Amyloidosis Cutis Dyschromica ^[1,2,5,14,17,18]	<ul style="list-style-type: none"> • AR • Early childhood • Mottled hyperpigmented and hypopigmented macules on the trunk, Limbs and face. • ⊗ Amorphous eosinophilic masses (amyloid) in the papillary dermis stained with Congo red. 	None
Xeroderma Pigmentosum ^[1,2,5,16,18,19,20]	<ul style="list-style-type: none"> • AR • Early childhood • Freckles, hyperpigmented macules, lentigens, atrophic hypopigmented macules on Sun-exposed sites. • Flat epidermis, irregular proliferation of rete reges, basophilic degeneration of dermal collagen. 	Photosensitivity, skin cancer, ocular and neurological features
Dyskeratosis congenital ^[2,4,6,7,8,9]	<ul style="list-style-type: none"> • X-linked, occasionally AD. • Early childhood. • Reticulated hyperpigmented and hypopigmented macules on neck, upper chest and upper arms. • pigmentary incontinence with melanophages in dermis. 	Telangiectasia, atrophy, palmoplantar hyperkeratosis, Pancytopenia, nail atrophy
Generalized Dowling–Degos disease ^[2,6,21,7,9,14]	<ul style="list-style-type: none"> • AD • Young adulthood • Mottled hyperpigmented and hypopigmented macule, papules on the trunk, limbs, flexural areas, over almost all body. • Mild hyperkeratosis, thinned epidermis, downward proliferation of rete ridges, basal hyperpigmentation. 	Facial pits, comedo-like lesions hidradenitis suppurativa, keratoacanthoma, mental retardation, epidermal or trichelimmal cysts.
Dermatopathia Pigmentosa Reticularis ^[1,4,8]	<ul style="list-style-type: none"> • AD • From birth to early childhood. • Generalized reticulated hyperpigmentation. 	non-scaring alopecia (of the scalp, eyebrows and axillae) and onychodystrophy. Additional association include loss of dermatoglyphic, hypo or hyperhidrosis, pigmented lesion of oral mucosa, wiry scalp hair and digital fibromatosis,

Naegeli–Franceschetti–Jadassohn syndrome [1,5,6,3,9]	<ul style="list-style-type: none"> • AD • From birth to early childhood. • Reticulate hyperpigmentation involving neck, flexural skin, perioral and periorbital areas. • Hyperkeratosis of the epidermis, dermal melanophage and Civatte bodies in areas of hyperpigmentation. 	Diffuse keratoderma, enamel hypoplasia, hyperhidrosis and nail dystrophy.
Reticulate Acropigmentation of Kitamura [6,9,14,21]	<ul style="list-style-type: none"> • AD • First and second decades. • Reticulate hyperpigmentation (freckles-like) on the dorsum of hands and feet, whole body may be involved. • Epidermal atrophy, increased number of basal melanocytes. 	Palmar pits, breaks in epidermal rete ridges, non-scarring alopecia
Epidermolysis Bullosa Simplex with Mottled Pigmentation [6,9,21,22]	<ul style="list-style-type: none"> • AD • Infancy • Mottled pigmentation on the trunk and limbs. • Intraepidermal blistering, focal hyperpigmentation of the basal layer with melanin incontinence. 	Nail dystrophy and hyperkeratotic papules over extensor surfaces of the extremities.
Chronic arsenic toxicity [2,7,23]	<ul style="list-style-type: none"> • Not inherited • Depends on the accumulation of arsenic in target tissues and its metabolism and elimination. • Guttate hypopigmentation superimposed on hyperpigmentation on the trunk, areola, flexural creases, any part of the body. • May be Increased melanin in epidermis, no melanocytic proliferation. 	Punctuate palmoplantar keratoderma, arsenical keratosis, Bowen's disease, squamous and basal cell carcinomas, Increased risk of internal malignancies.

AD =Autosomal dominant AR= Autosomal recessive

CONCLUSION

DUH was common disease in Ramadi city and was autosomal recessive inheritance and the skin clinical picture was not much different with what has been reported while there was no oral, hair and systemic involvement.

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